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Exosomal miRNA-106b from cancer-associated fibroblast promotes Gemcitabine resistance in pancreatic cancer

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Introduction : Gemcitabine (Gem)-based chemotherapy is commonly used to treat pancreatic ductal adenocarcinoma (PDAC). However, intrinsic and acquired resistance to Gem therapies remains a challenge for PDAC patients. Cancer-associated fibroblasts (CAFs), comprising the majority of the tumor bulk, play vital roles in regulating tumor progression and drug resistance by transferring exosomes (Exo) to cancer cells.

Methods : We investigated the potential role of CAFs in the resistance of pancreatic cancer cells to Gem and revealed its underlying mechanism.

Results : We found that CAFs were innately resistant to Gem. The conditioned medium (CM) and exosomes derived from CAFs contributed to Gem resistance of pancreatic cancer cells, and Gem treatment further enhanced the effect of CAFs or CAFs-Exo on pancreatic cancer cells survival. We identified that miR-106b level was upregulated in CAFs and CAFs-Exo following Gem treatment. And miR-106b was directly transferred from CAFs to the pancreatic cancer cells by the mediation of exosomes. Furthermore, pretreatment of CAFs with miR-106b inhibitor suppressed miR-106b expression in CAFs-Exo, and resulted in a decreased resistance of pancreatic cancer cells to Gem. Finally we identified that miR-106b promoted Gem resistance of cancer cells by directly targeting TP53INP1.

Conclusions : CAFs-mediated Gem resistance in PDAC is partially related to overexpression of miR-106b in CAFs-Exo and that inhibiting the transfer of CAFs-derived miR-106b might be a potential treatment to alleviate Gem resistance.

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